REVIEW

Utility of Ketone Supplementation to Enhance Physical Performance: A Systematic Review

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ABSTRACT

Ingesting exogenous ketone bodies has been touted as producing ergogenic effects by altering substrate metabolism; however, research findings from recent studies appear inconsistent. This systematic review aimed to aggregate data from the current literature to examine the impact of consuming ketone supplements on enhancing physical performance. A systematic search was performed for randomized controlled trials that measured physical performance outcomes in response to ingesting exogenous ketone supplements compared with a control (nutritive or non-nutritive) in humans. A total of 161 articles were screened. Data were extracted from 10 eligible studies (112 participants; 109 men, 3 women) containing 16 performance outcomes [lower-body power ($n = 8$) and endurance performance ($n = 8$)]. Ketone supplements were grouped as ketone esters ($n = 8$) or ketone salts/precursors ($n = 8$). Of the 16 performance outcomes identified by the systematic review, 3 reported positive, 10 reported null, and 3 reported negative effects of ketone supplementation on physical performance compared with controls. Heterogeneity was detected for lower-body power ($Q = 40$, $I^2 = 83\%$, $P < 0.01$) and endurance performance ($Q = 95$, $I^2 = 93\%$, $P < 0.01$) between studies. Similarly high levels of heterogeneity were detected in studies providing ketone esters ($Q = 111$, $I^2 = 93\%$, $P < 0.01$), and to a lesser extent studies with ketone salts/precursors ($Q = 25$, $I^2 = 72\%$, $P < 0.01$). Heterogeneity across studies makes it difficult to conclude any benefit or detriment to consuming ketone supplements on physical performance. This systematic review discusses factors within individual studies that may contribute to discordant outcomes across investigations to elucidate if there is sufficient evidence to warrant recommendation of consuming exogenous ketone supplements to enhance physical performance. *Adv Nutr* 2020;11:412–419.

Keywords: ketone ester, ketone salt, ketosis, ketogenic, β-hydroxybutyrate, endurance exercise, aerobic exercise, lower-body power

Introduction

It is well established that reduction in carbohydrate availability within skeletal muscle (i.e., glycogen) is associated with fatigue and impaired physical performance (1–3). As such, much focus has been directed toward the development of nutritional strategies for fuel use that spare endogenous carbohydrate during endurance exercise (4, 5). Ketone bodies have the potential to serve as an alternative substrate to carbohydrate during endurance exercise (6). Endogenous ketone bodies [e.g., acetoacetate, acetone, and β-hydroxybutyrate (βHB)] are derived from fatty acids in the liver and transported to peripheral tissues where they are oxidized for energy (7, 8). Habitual consumption of a ketogenic diet, which is high in fat (80% total kcal), very low in carbohydrate (5% total kcal), and moderate in protein (15% total kcal), increases circulating ketone bodies and fat oxidation, while decreasing carbohydrate oxidation during endurance exercise (8–10). However, despite alterations in substrate oxidation following ketogenic diets, there does not appear to be a clear benefit on enhancing physical performance (8, 10–12), possibly because severe carbohydrate restriction reduces muscle glycogen at the onset of exercise and impaired glycolytic flux during high-intensity exercise (11–13).

To avoid undesirable effects of carbohydrate restriction associated with ketogenic diets, exogenous ketone supplementation has been promoted as an alternative strategy to increase circulating ketone body concentrations (14, 15). Ketone supplements can induce acute ketosis, defined as

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Supplemental Tables 1 and 2 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/advances/.

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Abbreviations used: ES, effect size; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RER, respiratory exchange ratio; βHB, β-hydroxybutyrate.

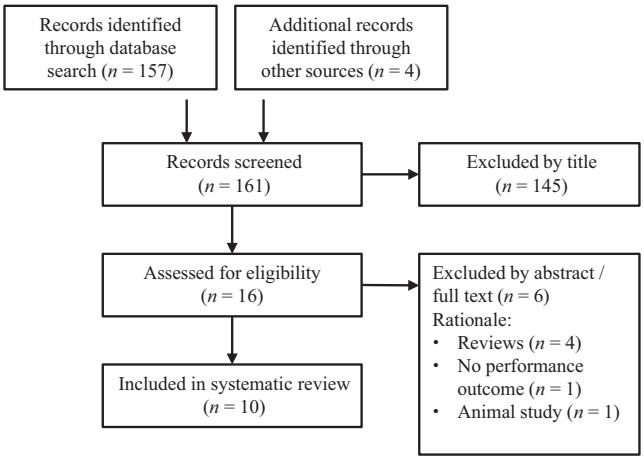

FIGURE 1 PRISMA systematic review search strategy diagram.

>0.5 mM βHB in blood, for up to 3 h after consuming a single dose without dietary modification (16, 17). Specifically, oral consumption of a ketone ester can acutely increase circulating βHB concentrations as high as 5 mM in healthy adults (16, 18, 19). βHB has been suggested to function as a signaling metabolite (20), acting independently of changes in macronutrient intake to alter substrate oxidation during exercise (18, 21). Most notably, Cox et al. (18) demonstrated that increases in circulating βHB concentration >2 mM with ketone supplementation immediately before endurance exercise decreases muscle glycogen use and increases intramuscular triglyceride use as a fuel source during endurance exercise. Furthermore, a 2% increase on distance traveled during a 30-min time period accompanied the shifts in substrate oxidation in that study (18). Although results from the study by Cox et al. (18) have garnered much excitement around the use of ketone supplements as an ergogenic aid, such robust improvements in physical performance have not been replicated in more recent studies (22, 23).

Discordant findings across studies make it difficult to form a clear conclusion regarding the efficacy of ketone supplementation to enhance physical performance. As such, the objective of this systematic review was to aggregate data from the current literature to discuss the potential impact of ketone supplementation on physical performance.

Methods

Literature search strategy

Abstracts of publications identified in Pubmed (http://www.ncbi.nlm.nih.gov/pubmed) were reviewed for relevance. The search took place on 12 February 2019 and was not restricted by publication date. Exact search terms are described in **Supplemental Table 1**. All terms were included in a single search. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) search strategy and subsequent reference narrowing is described in **Figure 1** (24). Reference lists from these publications were hand-searched for any reports missed by database searches. Four additional manuscripts were identified outside of the initial search. There were no language restrictions, although English search terms were used. Full-text publications were reviewed for relevance.

Inclusion criteria

Randomized crossover or parallel controlled trials assessing the impact of ketone supplements compared to nutritive or non-nutritive controls on physical performance outcome measures in humans were included in the current analysis. There were no exclusion criteria for study duration, ketone supplement type, ketone dose, or performance outcome measurement, nor participant's sex, age, body mass, sample size, or training status.

Exclusion criteria

Studies assessing the impact of ketone supplements on physical performance in animal models were excluded from the current analysis. Studies with ketogenic diets as their intervention to examine the impact of ketosis on physical performance were excluded. Studies comparing ketone supplements to a control for outcomes other than physical performance were excluded from the current analysis.

Bias and limitations

A bias analysis was performed according to PRISMA guidelines recommended by Moher et al. (24). Ratings of low, unclear, or high risk of selection, performance, attrition, and reporting bias were assigned for each study. The resulting risk of bias assessment is reported in **Supplemental Table 2**.

Data extraction

Data were extracted from 10 studies determined to meet the inclusion and exclusion criteria. Age, weight, and VO_{2max} were extracted from each study to provide descriptive characteristics of participants. Physical performance data were extracted from ketone and control groups. For single studies that reported multiple physical performance outcome metrics, data were grouped separately as subgroups. Peak blood or plasma βHB data were extracted in ketone supplement groups to assess whether concentrations exceeded the previously hypothesized 2 mM threshold required for performance enhancement (25, 26). Data that were not reported numerically were generated from provided figures by digitally measuring the height of histogram bars and calculating relative to measured *y*-axis units (27).

Meta-Essentials by Van Rhee (28) with Microsoft Excel 2010 (Microsoft Corp) were used to examine extracted data. Hedges' g was used to generate effect sizes (ESs) and 95% CI from individual studies (29). To determine heterogeneity both the Q and I^2 statistics were used to assess between-study variations in ES (29). Publication bias was determined with use of Egger regression (30). ES for differences in physical performance outcomes were determined as standard mean difference between ketone supplement compared to control divided by pooled SD. For visual representation of the data, forest plots with individual study ES were generated.

Physical performance was split into subgroups, as defined by original papers, as lower-body power (watts) and endurance performance (performance test with a time component; e.g., time to exhaustion, time trial, etc.). In addition, performance data were split into subgroups as ketone esters and ketone salts/precursors. Because of high heterogeneity and inconsistencies in the direction of effects across studies, accumulation of data into a single meta-analysis could not be conducted at this time (31). Performance data are presented as ES mean (95% CI). All other data are presented as means ± SDs.

Results

Study characteristics

Of the 161 studies captured by the initial literature search, 10 randomized controlled trials met the inclusion criteria of the current investigation (Figure 1). Within these studies, 16 performance outcomes (8 subgroups for lower-body power and 8 subgroups for endurance performance outcomes) were identified (**Table 1**). Ketone supplement type varied across studies, with 4 providing a ketone monoester (18, 32–34), 3 providing a ketone salt (23, 35, 36), 2 providing ketone precursors (37, 38), and 1 providing a ketone diester (22). A total of 112 individuals, 109 men and 3 women, participated in these studies (**Table 2**). No publication bias was detected of articles included in the meta-analysis ($P = 0.33$).

Heterogeneity across studies

The ability for ketone supplements to rapidly induce nutritional ketosis has garnered much attention as a potential alternative fuel source that may be used to enhance physical performance (15, 39, 40). However, of the 16 performance outcomes identified by this systematic review, 3 reported positive (18, 33, 36), 10 reported null (23, 32–38), and 3 reported negative (22, 23) effects of ketone supplementation on physical performance compared to controls. Discordant findings between studies resulted in a high level of heterogeneity for lower-body power ($Q = 40$, $I^2 = 83\%$, $P < 0.01$) and endurance performance ($Q = 95$, $I^2 = 93\%$, $P < 0.01$; **Figure 2**). Similarly high levels of heterogeneity were detected in studies providing ketone esters ($Q = 111$, $I^2 = 93\%$, $P < 0.01$), and to a lesser extent studies with ketone salts/precursors ($Q = 25$, $I^2 = 72\%$, $P < 0.01$; **Figure 3**). Large degrees in variations of outcome measures, potentially because of small sample size and methodological differences between studies, suggest that caution should be taken when interpreting overall results from the larger body of literature (31). As such, consideration must be given to factors that may result in divergent outcomes across studies.

Circulating βHB concentrations

Peak circulating βHB concentrations were associated ($r = 0.73$, $P < 0.05$) with the average gram dose amount between studies (**Figure 4**A). Dose amount explained 53% of the variance in circulating βHB concentrations. Remaining variance driving differences in circulating βHB concentrations across studies could be attributed to ketone supplement type and fed state (fed compared with fasted). Consuming ketone monoesters under fasting conditions resulted in peak circulating βHB concentrations above the 2 mM threshold in 3 studies (18, 32, 33) (Figure 4B). Although the remaining studies providing ketone salts (23, 35, 36), ketone diester (22), ketone precursors (37, 38), or ketone monoester under fed conditions (34) increased circulating βHB concentrations above controls, and induced acute ketosis (βHB >0.5 mM), they failed to cross the 2 mM threshold. These findings are consistent with work by Stubbs et al. (17), who reported βHB concentrations increase in a dose-dependent manner and that ketone monoester

TABLE 1 Description of ketone supplement, performance outcome, and exercise mode included in the systematic review[1]

Study	Group	Reference	Ketone supplement	Performance outcome	Mode
1	1	Cox et al., 2016 (18)[2]	R-3-hydroxybuty1-R 3-hydroxybutyrate monoester (576 mg/kg) + CHO (110 g) vs. CHO (isocaloric)	Distance traveled during 30 min time trial	Cycle ergometer
2	2	Leckey et al., 2017 (22)[2]	1,3-butanediol acetoacetate diester (500 mg/kg) vs. placebo	31.2 km time trial	Cycle ergometer
	3			Lower-body power	Cycle ergometer
3	4	Rodger et al., 2017 (35)[2]	β-hydroxybutyrate salt (11.7 g) vs. placebo	Lower-body power	Cycle ergometer
4	5	O'Malley et al., 2017 (23)[2]	β-hydroxybutyrate salt (300 mg/kg) vs. placebo	10 km time trial	Cycle ergometer
	6			Lower-body power	Cycle ergometer
5	7	Evans and Egan, 2018 (32)[2]	R-β-hydroxybutyrate-R 1,3-butanediol monoester (750 mg/kg) + CHO (90 g) vs. CHO (90 g)	20 m shuttle run time to exhaustion	Outdoor track
6	8	Waldman et al., 2018 (36)[2]	β-hydroxybutyrate salt (11.38 g) vs. placebo	Lower-body power	Cycle ergometer
	9			Fatigue index	Cycle ergometer
7	10	Shaw et al., 2019 (38)[2]	R,S-1,3-butanediol (350 mg/kg) vs. placebo	Time trial	Cycle ergometer
	11			Lower-body power	Cycle ergometer
8	12	Scott et al., 2019 (37)[2]	1,3-butanediol (500 mg/kg) + CHO (60 g) vs. CHO (isocaloric)	5 km time trial	Treadmill
9	13	Poffé et al., 2019 (33)[3]	R-3-hydroxybuty1-R 3-hydroxybutyrate monoester (25 g) + CHO/PRO (60 g/31 g) vs. medium-chain TGs (16.4 g) + CHO/PRO (60 g/31 g)	Lower-body power (30 min time trial)	Cycle ergometer
	14			Lower-body power (90 s isokinetic sprint)	Cycle ergometer
	15			Lower-body power (120 min endurance performance test)	Cycle ergometer
10	16	Evans et al., 2019 (34)[2]	R-3-hydroxybuty1 R-3-hydroxybutyrate monoester (573 mg/kg) + CHO (1 g/min exercise) vs. CHO (1 g/min exercise)	10 km time trial	Treadmill

[1] CHO, carbohydrate; PRO, protein.
[2] Acute crossover randomized controlled trial.
[3] Chronic (3-wk) parallel randomized controlled trial.

TABLE 2 Characteristics of study participants included in the systematic review[1]

Reference	Population description	Sample size	Age, y	Weight, kg	VO_{2max}, mL/(kg·min)
Cox et al., 2016 (18)	Elite cyclists	8 (6 M, 2 F)	29 ± 1	85 ± 5	—
Leckey et al., 2017 (22)	Elite cyclists	10 (10 M, 0 F)	25 ± 7	74 ± 8	71 ± 6
Rodger et al., 2017 (35)	Trained cyclists	12 (12 M, 0 F)	35 ± 8	75 ± 8	68 ± 7
O'Malley et al., 2017 (23)	Healthy adults	10 (10 M, 0 F)	23 ± 3	83 ± 13	45 ± 10
Evans and Egan, 2018 (32)	Team sport athletes	11 (11 M, 0 F)	25 ± 5	79 ± 5	54 ± 2
Waldman et al., 2018 (36)	Healthy adults	15 (15 M, 0 F)	23 ± 2	81 ± 9	—
Shaw et al., 2019 (38)	Trained cyclists	9 (9 M, 0 F)	27 ± 5	70 ± 8	64 ± 3
Scott et al., 2019 (37)	Trained runners	11 (11 M, 0 F)	38 ± 12	67 ± 7	64 ± 5
Poffé et al., 2019 (KE, 33)	Healthy adults	9 (9 M, 0 F)	21 ± 2	73 ± 7	56 ± 6
Poffé et al., 2019 (CON, 33)	Healthy adults	9 (9 M, 0 F)	21 ± 3	75 ± 11	55 ± 6
Evans et al., 2019 (34)	Trained runners	8 (7 M, 1 F)	34 ± 7	69 ± 10	62 ± 6

[1]Values are means ± SDs. —, indicates data not reported in primary manuscript. CON, control; KE, ketone ester.

results in greater acute increase in βHB concentrations (2.8 mM) compared to a ketone salt (1.0 mM). This past work also showed that elevations in βHB concentrations were blunted when ketone monoesters were consumed in the fed (2.2 mM) state compared with the fasted (3.3 mM) state. Together these results indicate that to maximize increases in circulating βHB concentrations, higher amounts of ketone monoesters should be consumed under fasting conditions.

Physical performance and ketone supplement type

The absence of an ergogenic effect with ketone supplementations in some studies included in the current systematic review may be a result of discrepancies in pharmacokinetics of variant ketone compounds used across investigations. As described above, studies providing a ketone salt/precursor all failed to cross the 2 mM circulating βHB concentration threshold. Of the 8 performance outcome measures from these investigations, only 1 was reported as being significantly improved with ketone supplementation compared to controls (36). The remaining 7 performance outcome measures reported either a null (35–38) or negative (23) effect of ketone supplementation compared to controls (Figure 3). It is important to note that the 1 performance outcome that was significantly improved with ketone supplementation, fatigue index (watts per second), was derived from power

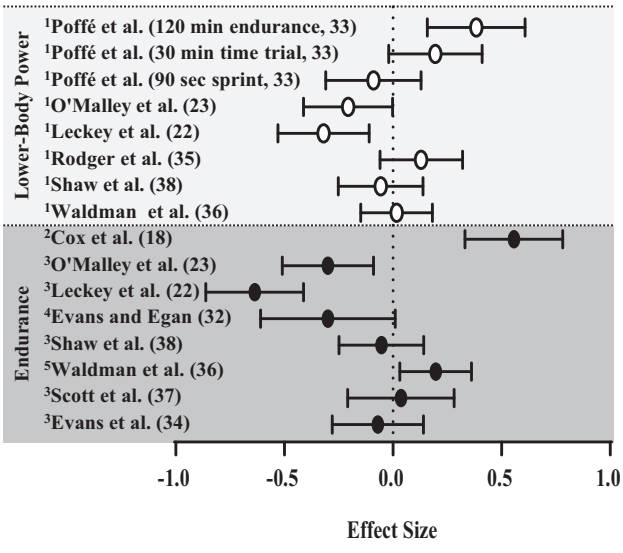

FIGURE 2 Values are effect size (ES), 95% CI. Data derived from healthy participants consuming a ketone supplement or control to determine impact on physical performance. Individual white circles represent the ES of power outcomes. Individual black circles represent the ES of endurance performance outcomes involving time. [1]Lower-body power, [2]distance traveled in 30 min, [3]time trial, [4]shuttle run time to exhaustion, [5]fatigue index.

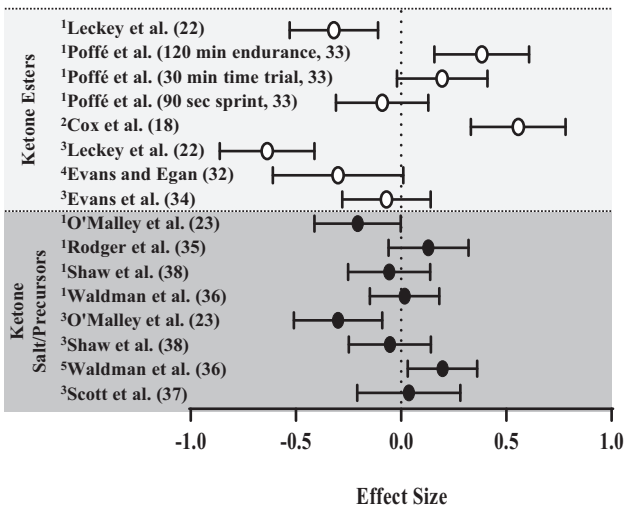

FIGURE 3 Values are effect size (ES), 95% CI. Data derived from healthy participants consuming a ketone supplement or control to determine impact on physical performance. Individual white circles represent the ES of ketone esters. Individual black circles represents the ES of ketone salts/precursors. [1]Lower-body power, [2]distance traveled in 30 min, [3]time trial, [4]shuttle run time to exhaustion, [5]fatigue index.

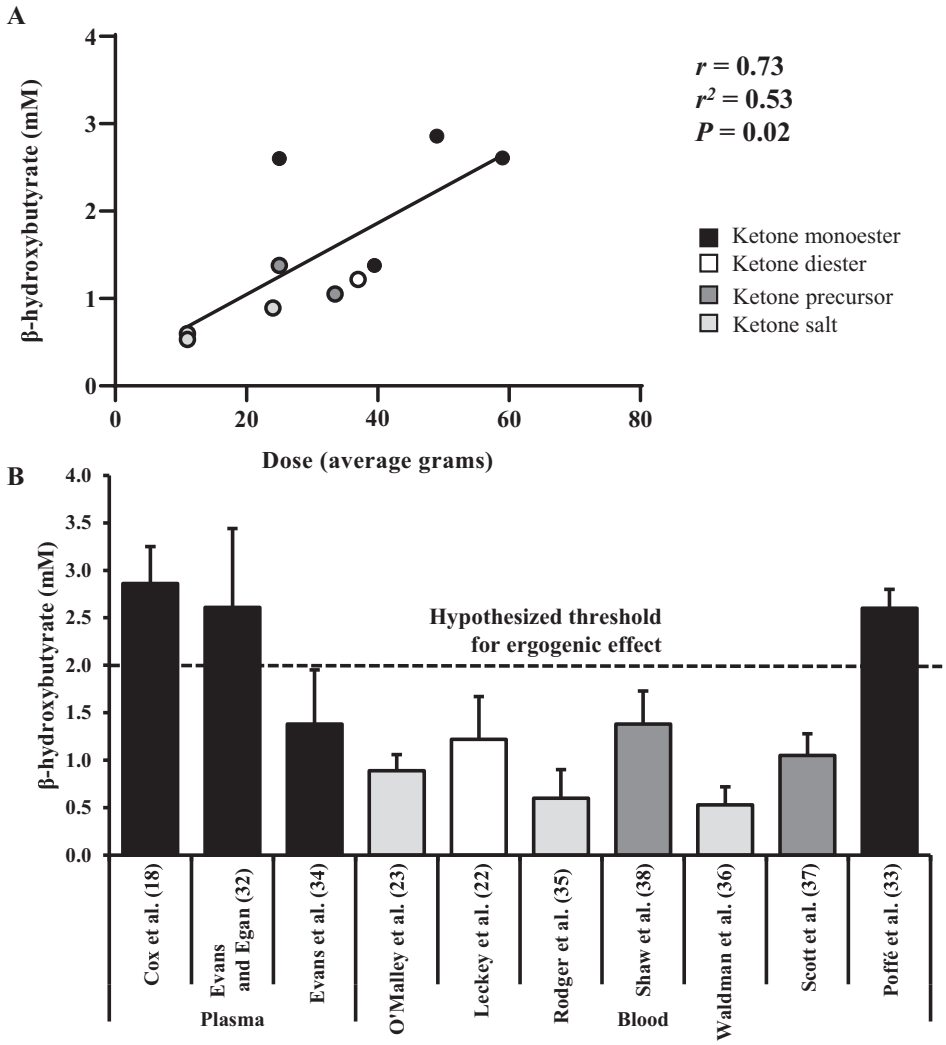

FIGURE 4 Association of peak β-hydroxybutyrate concentration and ketone supplement dose (A). Values are means ± SDs for peak concentrations of β-hydroxybutyrate in plasma and blood (B). Dotted line represents hypothesized threshold that β-hydroxybutyrate concentrations must cross to induce an ergogenic effect on physical performance (25). Data derived from healthy participants consuming a ketone supplement.

output during a Wingate test that was not statistically different between groups (36). This resulted in the authors of this previous study to conclude that ketone salt supplementation did not improve physical performance (36). Similar conclusions of no physical performance benefit with ketone salt/precursor supplementation were stated by all authors of these past investigations (23, 35–38).

Physical performance outcomes in studies providing ketone esters have a greater degree of variance (I^2 = 93%) compared to studies providing ketone salts/precursors (I^2 = 72%; Figure 3). Investigations of ketone esters reported positive (18, 33), null (32–34) or negative (22) effects across 8 outcome measurements. Discrepancies between studies may, in part, be explained by ketone ester type and circulating βHB concentrations. Two studies that reported performance benefit with ketone supplementation provided ketone monoesters and increased circulating βHB concentrations above the 2 mM threshold (18, 33). Conversely, ketone supplementation had a negative effect in 1 study in which participants consumed a ketone diester and circulating βHB concentrations did not cross the 2 mM threshold (22). The form of the ketone ester (monoester vs. diester) may thus impact the utility of the supplement on physical performance improvement. As will be discussed in a later section, ketone diesters have been suggested to have low palatability and gastrointestinal tolerability which may have contributed to its negative impact on physical performance (26).

Consumption of exogenous ketone monoesters in fed compared with fasted state may also alter their impact on physical performance. Evans et al. (34) reported that consuming a ketone monoester in the fed state resulted in a failure of circulating βHB concentrations to increase above the 2 mM threshold. Along with lower elevations in βHB concentrations, ketone monoester consumption

had a null effect on physical performance compared to the control (34). Delayed gastric emptying of the ketone monoester with food consumption appeared to blunt acute ketosis (17), which may potentially impair performance benefit.

While the form and discrepancy in circulating βHB concentrations may explain some discordant results, these factors do not explain all variance between ketone ester studies. Specifically, 2 studies that provided a ketone monoester and increased circulating βHB concentrations above the 2 mM threshold, independent of dose, reported null effects on physical performance compared to controls (32, 33). This suggests that elevations in circulating βHB concentrations do not independently improve physical performance, and other factors must be considered when examining the utility of ketone supplements.

Performance test

One factor that may influence the impact that ketone supplementation has on physical performance is the type of test being conducted. Ketones have been suggested to be antiglycolytic (18). Reducing reliance of glycogen use may have advantageous effects when performing sustained low-to-moderate-intensity endurance exercise (15). However, if exercise is higher in intensity, impairing glycolytic flux may be detrimental to physical performance. Cox et al. (18), observed improvement in distance traveled during a 30-min time period with ketone monoester plus carbohydrate compared to carbohydrate only. Conversely, Evans and Egan (32) reported no difference between ketone monoester and control in time to exhaustion during 20-m shuttle runs. Potential impairment of glycolysis with exogenous ketone consumption may have contributed to the lack of performance benefit during more high-intensity sprint work (14). In agreement with this, O'Malley et al. (23) reported that ketone salt supplementation resulted in a 7% reduction in lower-body power compared to a non-nutritive control, which the authors attributed to potential inhibition of glycolysis. Results from Poffé et al. (33) appear to corroborate this theory, as lower-body power was not different during a 90-s sprint test, but was higher during the final 30 min of a 120-min endurance performance test with ketone monoester supplementation compared to control (Figure 2). However, caution should be taken when interpreting endurance performance results from Poffé et al (33). Unlike the 90-s sprint and 30-min time trial tests, which were reported as longitudinal changes during this 3-wk study, the 120-min endurance performance test appears only as a cross-section result on study day 18. With no baseline data, it is difficult to determine whether differences in endurance performance are the result of the ketone supplement or inherent to the participants in the groups. In addition, participants in the ketone group in work by Poffé et al. (33) consumed more energy and carbohydrate during the intervention compared to the control group. Differences in dietary intake between groups may have confounded results, limiting the investigators' ability to isolate the effects of ketone supplementation on physical performance. Regardless, these findings suggest that consideration should be given to the intensity of the physical activity being performed to determine the utility of a ketone supplement.

Shifts in substrate metabolism

Although some studies in the current systematic review reported shifts in substrate metabolism that would indicate a sparing of endogenous glucose stores with ketone supplementation (18, 23), others reported no change in markers of substrate metabolism (22, 33–38). Insufficient sparing of endogenous glucose may explain the lack of performance benefit with ketone supplements. Poffé et al (33), reported no difference in muscle glycogen content between ketone and control groups in their 3-wk study. It should be noted that muscle glycogen was reported with use of the tissue wet weight, rather than dry weight (33). Variations in body water may increase the variability, and thus the accuracy of this measurement. Several other investigations observed no acute differences in blood lactate concentrations (34, 36–38) or respiratory exchange ratio (RER) (22, 34–38) during submaximal exercise between ketone supplements compared to controls. There are limitations when relying solely on circulating lactate concentrations and RER for assessment of metabolic alterations with ketone supplementation. Although lower circulating lactate concentrations may indicate lower rates of glycolysis, this does not necessarily provide information on lactate production rate and clearance by skeletal muscle (41). In addition, the RER of βHB is 0.89, making it difficult to interpret the impact of ketone bodies on substrate oxidation with use of conventional respiratory gas exchange measures (42). In a study by Evans et al. (21), RER was higher following ketone supplementation during lower intensity exercise (<60% VO_{2peak}) compared to a non-nutritive control. Higher RER during exercise is typically associated with increased carbohydrate and reduced fat oxidation (43). Because RER cannot isolate ketone oxidation, reliance on indirect calorimetry alone does not provide a clear understanding of the impact of ketone supplementation on alterations in substrate metabolism. Although it appears the majority of studies in this systematic review did not show alterations in substrate metabolism with ketone supplementation, there is a need to conduct a more thorough examination of substrate metabolism. Direct examination of muscle metabolism or use of stable isotopes, which allows for tracing the kinetics of a single nutrient, such as glucose and lactate, are more appropriate methodologies for assessing the influence of ketone supplements on substrate oxidation.

Gastrointestinal distress

Potential performance enhancements may have also been negated by the common side effect of gastrointestinal distress associated with ketone supplementation. Symptoms ranging from mild to moderate severity have been reported, including flatulence, nausea, diarrhea, constipation, vomiting, abdominal distress, and abdominal pain (16). Although not

measured in all studies, high rates of gastrointestinal distress (~80% of participants) were reported in 2 studies (32, 38) that found no performance benefit and 1 study (22) reported a negative effect of ketone supplementation on physical performance compared to control. The ergolytic response of consuming a ketone diester reported by Leckey et al. (22) can most likely be attributed to all 10 participants reporting some form of gastrointestinal discomfort including dry retching, nausea, reflux, vomiting, and dizziness. The inability for individuals to tolerate these adverse effects of ketone supplements may negate their potential for performance enhancement.

Considerations for future research

High heterogeneity of the current ketone supplement literature can at least, in part, be explained by relatively low samples size of studies, variant ketone supplement type, dose, performance outcome, alterations in substrate metabolism, and gastrointestinal distress. Future studies should consider these factors in an attempt to reduce the overall heterogeneity of the field. Because of the overall null effects on performance outcomes and lower elevations in circulating βHB concentration, there is insufficient evidence to warrant the use of ketone salts/precursors to enhance physical performance. Based on the current understanding of ketone compound pharmacokinetics (16, 17, 19), alteration in substrate metabolism (18), and performance benefit (18, 33), ketone monoesters appear to be the best candidate moving forward. To gain greater insight into the impact of ketone monoester supplementation on physical performance, future investigations should focus on prolonged endurance events or perform a battery of performance tests to isolate during which events the supplement may or may not show benefit. All future work should assess gastrointestinal distress to determine whether an individual's tolerance of the supplement confounds performance results. Complex analysis of substrate metabolism, with stable isotope methodologies and direct assessment of skeletal muscle is needed to gain a greater understanding of the impact of these products on substrate use.

Conclusions

In conclusion, results from this systematic review show equivocal effects of ketone supplementation across studies. Out of 16 identified performance outcomes, 3 positive, 10 null, and 3 negative effects were reported comparing ketone supplements to controls. Discrepancies in performance outcomes may be caused by ketone supplement type, dose amount, and performance outcome test. The high level of heterogeneity and inconsistent direction in outcome measures between studies means there is presently insufficient evidence to conclude recommendation of consuming ketone supplements on physical performance improvement.

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